

which must be deleted or inserted." The Examiner continued by stating that "[d]ue to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation."

Applicants respectfully traverse this rejection and request reconsideration.

The Examiner asserts that while it would appear that techniques are known in the art for inactivation of genes, it is not routine to screen for positions within the DNA sequence of the gene so that it does not invade the cells, does not spread within infected cells, or does not produce toxins.

Applicants respectfully submit that the Examiner is applying an improper test of enablement. The test for enablement is whether one skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art* without undue experimentation. (M.P.E.P. § 2164.01; italics added.) Although some experimentation may be necessary to carry out the claimed invention, the experimentation would not be undue, but merely routine.

Applicants submit herewith prior art references that clearly indicate the level of skill in the art prior to the filing of the instant application. (Exhibits 1-3.) Nassif et al. teaches assay procedures for screening for *Shigella* mutations that affect invasion of cells (page 1694, second column, paragraph 3), toxin production (page 1694, second column, paragraph 4), and spread (page 1694, second column, paragraphs 5 and 6). (Exhibit 1.)

Baudry et al. teaches assay procedures for screening for *Shigella* mutations that affect invasion of cells (page 3405, paragraph 3) and toxin production (page 3405, paragraph 4). (Exhibit 2.)

Maurelli et al. teaches assay procedures for screening for *Shigella* mutations that affect invasion of cells (page 2820, second column, paragraph 4), toxin production (page 2821, first column, paragraph 1), and spread (page 2821, first column, paragraph 1). (Exhibit 3.)

Applicants submit that these references teach the requisite screening procedures for identifying *Shigella* genes involved in the invasion of cells, spread within infected cells, and toxin production, which are used in the practice of applicants' invention. One skilled in the art recognizes that these references teach the requisite screening procedures, regardless of the fact that these techniques are performed on cells mutated by transposon mediated mutagenesis.

The Examiner states that the Nassif reference is only directed to an iuc::TN10 mutant and appears not to consider this reference as relevant to enablement. Applicants disagree.

Applicants submit that the specification teaches that, using the method of the invention, genes of *Shigella* can be wholly or permanently inactivated in a **conventional manner** and that the disclosed method is preferred over that of transposon mediated inactivation. (Specification, pages 5-6, bridging paragraph.) One skilled in the art recognizes that the "conventional manner" refers, in part, to those techniques routinely used in the art to inactivate genes by transposon mediated inactivation. Therefore, prior art disclosing the routine methods of screening for mutants in *Shigella* genes involved the invasion of cells, spread within infected cells, and toxin

production using transposon mediated mutagenesis are clearly relevant to the enablement provided by the instant application.

Regardless of whether it is common to screen for mutants in genes, the techniques for such screening are readily available to the skilled artisan and, in combination with the guidance of the specification, enable the skilled artisan to make and use the claimed invention. Applicants submit that the Examiner has unfairly dismissed the teachings of Nassif et al., Baudry et al., and Maurelli et al. as teaching screening methods for *Shigella* genes involved in the invasion of cells, spread within infected cells, and toxin production.

Furthermore, applicants submit that once a gene is mutated and identified, one skilled in the art can clone the gene by methodology known to the skilled artisan. Maurelli et al. is provided as an example of the prior art indicating the cloning of a gene involved in virulence. The identification of positive clones in this reference involved a simple antibiotic selection. Therefore, the skilled artisan can identify and clone *Shigella* genes responsible for the invasion of cells, spread within infected cells, and toxin production using the teachings of the prior art. The cloning of the mutated gene itself identifies a mutation capable of inactivation of gene expression. That is, the fact that a the cloned gene is "mutated" defines a disruption of the gene sufficient to inactivate expression. The replacement of transposon sequences with alternative non-mobile sequences would be expected by the skilled artisan to result in a similar inactivation of gene expression. A gene inactivated in this manner can be used in the practice of the instant invention.

Moreover, the specification teaches a method for inactivating genes. The specification

teaches one skilled in the art that the exact position of the mutation is irrelevant, as long as the mutation causes permanent inactivation of the gene. (Specification, page 5, lines 8-36, page 6, lines 1-17.) The specification repeatedly requires that the genes necessary for invasion, spreading, and toxin-production, be "wholly or partly removed or permanently inactivated, preferably at least partly removed." (Specification, page 5, lines 26-28, lines 30-34, line 36, page 6, line 1). One skilled in the art would not need to know which regions of the genes are responsible for activating or the number of nucleotides that must be deleted or inserted; the skilled artisan could use routine experimentation to remove the entire gene or mutate the gene in such a way as to eliminate protein production by the gene (e.g. frameshift mutation). One skilled in the art recognizes that insertion of non-coding DNA into most sites within the coding region of a *Shigella* gene would be expected to lead to inactivation of the gene. As such, one skilled in the art would recognize that mutations that eliminate gene expression are expected using the claimed invention.

To establish a *prima facie* case of non-enablement, the Examiner must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one skilled in the art to make and use the claimed invention. Applicants submit that a *prima facie* case of non-enablement has not been established.

According to M.P.E.P. 2164.05, in making the determination of enablement, the Examiner shall consider the original disclosure and all the evidence in the record, weighing evidence that supports enablement against evidence that the specification is not enabling. Applicants respectfully submit that, the since no evidence has been provided by Examiner to establish a case

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of non-enablement, it would be improper to reject the disclosure as non-enabling. If the Examiner is basing non-enablement on some personal knowledge of the Examiner, applicants urge the Examiner to make a disclosure of such information by means of an Affidavit or Declaration.

In the absence of any evidence of non-enablement, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusions

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. If the application is not allowed, applicants respectfully request that this response be entered for purposes of appeal because it clarifies issues for appeal.

Applicants believe that any extension of time required under 1.136(a) to file this paper is accounted for by the Petition for Extension of Time filed concurrently herewith. However, if a further extension is required, such extension is hereby requested and any additional fees required under 37 C.F.R. §§ 1.16 or 1.17 in connection with the filing of this Notice of Appeal, should be charged to Deposit Account No. 06-0916.

Respectfully submitted,

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